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Postoperative Ambulatory Status Predicts Survival in Patients with Glioblastoma Multiforme

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Abstract

Introduction: Much attention in the surgical literature has emphasized the survival benefit of maximal resection in patients with Glioblastoma Multiforme (GBM). Preoperative functional status has also been long recognized as a major factor on prognosis, but less attention has been paid to the importance of postoperative neurological function on survival. Our study sought to investigate the survival impact of a particularly severe postoperative motor deficit, the loss of functional ambulation, on survival in patients with newly diagnosed primary GBM.

Methods: We conducted a retrospective analysis of patients with lesions located in, or proximal to, the motor strip treated from 1999-2003 at our centre for whom complete pre- and post-operative data on ambulatory status was available. Demographic and treatment data including extent of resection, radiation, chemotherapy as well as survival data were collected. A multivariate Cox proportional hazards model was used to assess the impact of demographic/treatment variables and post-operative ambulatory status on survival.

Results: Overall 41 patients met inclusion criteria. The average age of patients included was 61 years, and 61% were men. Patients who were non-ambulatory post-operatively (n=10) tended to be older and were less likely to have received adjuvant chemotherapy. Chemotherapy and age were not significantly associated with survival in our sample. In the final model, the ability to ambulate at the first post-operative visit was associated with a hazard ratio of 0.1 (95% CI: 0.03 – 0.3, p<0.0001) and gross total resection was associated with a hazard ratio of 0.43 (95% CI: 0.2 – 0.94, p=0.04).

Conclusion: Among patients with primary GBM who are able to ambulate pre-operatively, a new pre-operative motor deficit that renders them non-ambulatory is associated with significantly worsened survival. For patients with lesions near motor cortex the benefits of additional tumor resection must be carefully weighed against the risk of a postoperative loss of ambulation.

Keywords

Gliomas; Glioblastoma; Survival; Ambulatory status; Ambulation; Prognosis; Extent of resection

Introduction

Glioblastoma Multiforme (GBM) is the most common primary neoplasm of the brain parenchyma and has a dismal prognosis. Patients diagnosed with GBM have a median survival of less than two years despite surgical resection, radiotherapy, and chemotherapy [1]. The surgical literature on GBM has increasingly focused on the benefit of increasing extent of resection, with large prospective and retrospective studies suggesting a significant benefit to increased surgical resection [2-5]. However, there is also evidence that increased resection must be balanced against avoidance of post-operative neurological deficits, as there is evidence that post-operative motor deficits reduce survival, and may in fact be more important predictors of survival than pre-operative deficits [6]. Reported rates of postoperative motor deficits range from 6-9% and overall worsening of functional status in 8-39% [6-13]. These deficits may be an important and potentially avoidable source of reduced survival in patients with GBM.

Pre-operative functional status, typically defined by the Karnovsky Performance Scale (KPS), has long been recognized as an important predictor of outcome in patients with GBM [5,14,15], however the importance of post-operative neurological function has received less attention. Despite recent guidelines suggesting "maximal safe resection" [16], the effect of postoperative deficits is poorly defined, and without this data, it is difficult for surgeons to balance a risk of creating a post-operative deficit with the potential benefit of increased tumor resection.

We sought to investigate the impact on survival of a particularly debilitating post-operative neurological deficit, loss of ambulation, in patients with glioblastoma. We hypothesized that the loss of ambulation would be associated with significantly worsened survival, even controlling for extent of resection and other confounding variables.

Methods

All chart review was performed with IRB approval. Charts were retrospectively reviewed for all adult patients with histologically confirmed primary glioblastoma Multiforme (GBM) admitted to the Hospital of the University of Pennsylvania for surgical resection between 1999 and 2003 for whom full details of their pre-operative and post-operative ambulatory status were available in the medical record and who were ambulatory preoperatively. Ambulatory status was recorded using the Cooper Scale [17]. The patient population was then dichotomized based on ability to ambulate post-operatively (Cooper 0-2 were considered ambulatory) assessed at the first outpatient post-surgical visit at 4-6 weeks post-operatively. Demographic information, extent of resection (by surgeon notes and post-operative imaging), and details of adjuvant therapies (chemotherapy and radiation therapy) were collected. Survival was calculated from date of diagnosis until date of death (located either in the patients' medical records or via the Social Security Death Index.

All statistical analyses were performed with Stata v11.2 (StataCorp, College Station, TX). Demographic and treatment data were compared between groups using the Wilcoxon rank sum (Mann-Whitney) for non-parametric data. Survival was compared using Kaplan-Meier curves and the log-rank test. The effect of confounders was addressed using multivariate Cox proportional hazards analysis. A p-value of <0.05 was considered significant for all analyses.

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Results

Overall 41 patients met inclusion criteria. The demographic and treatment characteristics of the patients are summarized in Table 1. The average age of patients included was 61 ± 12 years, and 61% were men. Patients who were non-ambulatory post op tended to be older (69 ± 13 years *vs.* 58 ± 11 years, p=0.02). Patients who were non-ambulatory postoperatively had a trend towards lower rates of gross total resection, though this trend was not significant. All patients in the study received post-operative external beam radiotherapy; however patients who were non-ambulatory postoperatively were far less likely to receive chemotherapy (29% *vs.* 87%).

Patients who were ambulatory post-operatively had improved 6-month and 1-year survival compared to those who were non-ambulatory (Table 1). Kaplan-Meier curves for patients stratified by post-operative ambulatory status are presented in Figure 1. Median survival in the ambulatory group was 52 weeks and for the non-ambulatory group was 20 weeks (p<0.0001).

Cox proportional hazards analysis was used to assess the impact of post-operative ambulatory status, age, gross total resection, and adjuvant chemotherapy on survival. In univariate analysis post-operative ambulatory status and gross total resection were significantly associated with survival, whereas patient age and adjuvant chemotherapy were not. Post-operative ambulatory status and gross total were then evaluated in a multivariate cox proportional hazards model and both were independently and significantly associated with improved survival. In the final model, the ability to ambulate at the first post-operative visit was associated with a hazard ratio of 0.1 (95% CI: 0.03 – 0.3, p<0.0001) and gross total resection was associated with a hazard ratio of 0.43 (95% CI: 0.2 – 0.94, p=0.04) (Tables 2 and 3).

Discussion

We found a significant association between post-operative ambulatory status and outcome in patients with primary GBM who were able to ambulate pre-operatively. This result needs to be considered in patients with GBMs near motor cortex and weighed against the benefit of additional marginal resection in these patients. In our analysis, the loss of the ability to walk as a consequence of glioma resection was associated with a larger proportional effect on survival than the extent of resection. Interestingly, though there was no significant difference in extent of resection between groups, there was a trend towards larger resections in the ambulatory group. This may suggest that the post-operative deficits observed were not the result of pursuing aggressive resection at the expense of risk of neurological deficit.

This study has a number of limitations. First, it is a retrospective study and subject to biases, particularly selection bias. Second, because the study was performed retrospectively, patients' assessments were performed by the primary neurosurgeon and their team and were not standardized or blinded. Third, the ambulatory and non-ambulatory groups were not well matched on age, and there were significant differences in patients receiving chemotherapy between the groups. Though we attempted to correct for these imbalances using multivariate analysis, both age and adjuvant chemotherapy are associated with survival in multiple prior studies and this may bias our analysis. However, functional status may be a requirement to receiving adjuvant therapy. The lack of adjuvant therapy may be a consequence of our primary independent variable, rather than a

Table 1: Patient characteristics.

	Study Population (n=41)	Ambulatory Postop (n=31)	Nonambulatory Postop (n=10)	p
Age at diagnosis	61 ± 12	58 ± 11	69 ± 13	0.02
% Male	61%	64%	50%	0.42
% Biopsy only	11%	11%	11%	0.97
% GTR	70%	75%	56%	0.27
% XRT	100%	100%	100%	1
% chemotherapy	69%	79%	29%	0.01
Median survival*	44 weeks	52 weeks	20 weeks	<0.0001
6-month survival	76%	87%	40%	0.003
1-year survival	36%	48%	0%	0.006

Legend: GTR = gross total resection; XRT = received external beam radiotherapy; chemotherapy = received adjuvant chemotherapy
p-values presented for Wilcoxon rank-sum test for all values except median survival compared by the log-rank test.

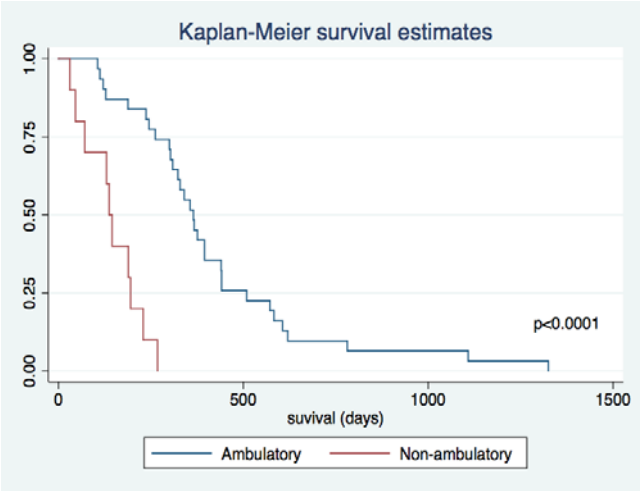

Figure 1: Comparison of survival in patients with GBM by post-operative ambulatory status.

Table 2: Univariate cox proportional hazards analysis.

Variable	Hazard Ratio	95% CI	p
Ambulatory postop	0.11	0.04 – 0.3	<0.0001
Age	1.01	0.98 – 1.04	0.32
Gross total resection	0.44	0.21 – 0.94	0.04
Adjuvant chemotherapy	0.81	0.39 – 1.69	0.57

Legend: CI = confidence interval

Table 3: Multivariate cox proportional hazards analysis.

Variable	Hazard Ratio	95% CI	p
Ambulatory postop	0.10	0.03 – 0.3	<0.0001
Gross total resection	0.43	0.20 – 0.94	0.04

Legend: CI = confidence interval

confounder. Finally, patients were not matched one side or eloquent tumor location and data on tumor size was not collected. We cannot draw conclusions about causality in a retrospective study and it is possible we are seeing an epiphenomenon where patients with larger tumors in more eloquent cortex were more likely to be non-ambulatory post-operatively and more likely to do poorly. We hope to address these methodological limitations in future studies.

Despite its limitations, we believe this small, retrospective study provides compelling evidence that post-operative ambulatory status is highly associated with survival in patients with primary GBM who are ambulatory pre-operatively. This data should inform surgeons' preoperative planning for patients with likely GBMs located in or near motor cortex. This analysis is not intended to challenge the excellent work emphasizing the value of extent of resection in patients with GBM. Rather, when pursing "maximal safe resections" these data are a reminder that "safe" may be as important as "maximal".

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